

APR 19/06 1-2-05

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

1. CERTIFICATE NUMBER: 43-R-0048

CUSTOMER NUMBER: 1461

FORM APPROVED
OMB NO. 0579-0036

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

University Of Missouri-Columbia
205 Jesse Hall
Columbia, MO 65211

Telephone: (573) -882-9500

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3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, or experimentation, or held for these purposes. Attach additional sheets if necessary)

FACILITY LOCATIONS (Sites) - See Attached Listing

b2 high, b7F

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (Attach additional sheets if necessary or use APHIS Form 7023A)

A. Animals Covered By The Animal Welfare Regulations	B. Number of animal being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results or interpretation of the teaching, research, experiments, surgery, or tests. (An explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used must be attached to this report)	F. TOTAL NUMBER OF ANIMALS (COLUMNS C + D + E)
4. Dogs	177	40	313	0	353
5. Cats	39	0	6	0	6
6. Guinea Pigs	0	20	0	0	20
7. Hamsters	0	10	283	0	293
8. Rabbits	0	32	147	6	185
9. Non-human Primates	0	0	0	0	0
10. Sheep	0	0	0	0	0
11. Pigs	100	390	331	0	721
12. Other Farm Animals	0	0	0	0	0
13. Other Animals					

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ASSURANCE STATEMENTS

- Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, testing, surgery, or experimentation were followed by this research facility.
- Each principal investigator has considered alternatives to painful procedures.
- This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). A summary of all such exceptions is attached to this annual report. In addition to identifying the IACUC-approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.
- The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

RESEARCH FACILITY OFFICIAL
(Responsible Institutional Official)

OFFICIAL OR INSTITUTIONAL OFFICIAL (Type or Print)

DATE SIGNED

(b)(6), (b)(7)(C)

(b)(6), (b)(7)(C)

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(b)(6), (b)(7)(C)

Column E Explanation

This form is intended as an aid to completing the Column E explanation. It is not an official form and its use is voluntary. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A Column E explanation must be written so as to be understood by lay persons as well as scientists.

1. Registration Number: 43-R-0048

2. Number 6 of animals used in this study.

3. Species (common name) Rabbit of animals used in the study.

4. Explain the procedure producing pain and/or distress.

See Attached Sheet

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5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below)

See Attached Sheet

6. What, if any, federal regulations require this procedure? Cite the agency, the code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

Agency _____ CFR _____

Number of rabbits used between October 1, 2004 and September 30, 2005.

6

Explain the procedure producing pain and/or distress.

Colorectal distension is a model of visceral pain that is commonly used in human volunteers as well as conscious rabbits. We have recently evaluated the physiological effects of colorectal distension in chronically instrumented, anesthetized and conscious rabbits. Colorectal distension was chosen as a nociceptive stimulus for use in conscious, chronically instrumented rabbits because it met the following criteria. Colorectal distension: 1) is titratable (i.e. variable intensity); 2) is short-lived (only present while the stimulus is "on"); 3) is repeatable; 4) increases arterial blood pressure approximately 10 mmHg; 5) does not cause tissue damage; 6) is responsive to opioid analgesia; and 7) is feasible in our conscious, chronically instrumented rabbit preparation. This project was done to evaluate the effect of colorectal distension on cardiovascular and respiratory responses to environmental stress and blood loss.

Prior to the first colorectal distension experiment, all rabbits underwent training to become accustomed to 1) being placed on their backs, and 2) colorectal balloon catheter placement. Training sessions were performed for at least one week prior to beginning colorectal distension experiments, and subsequently on each day preceding an experiment. Placement of the colorectal balloon catheter was facilitated by covering the rabbit's eyes and placing it on its back until it becomes relaxed (≤ 5 minutes). A well-lubricated colorectal balloon catheter is inserted 8 cm into the rectum and gently secured to the rabbit's tail. Following insertion of the colorectal balloon catheter, the rabbit was placed in a rabbit box. The rabbit was connected to monitoring equipment (respiratory and cardiovascular parameters). Following an equilibration period, the colorectal balloon is inflated slowly with distilled water. The end-point for colorectal distension was an increase in mean arterial pressure of approximately 10 mmHg above baseline. The distension pressure in the colorectal balloon did not exceed 90 mmHg. In our experiments, colorectal balloon distension pressures of approximately 54 mmHg were sufficient to raise mean arterial pressure by 10 mmHg. Importantly, pretreatment with buprenorphine virtually abolished the increase in arterial pressure at the same balloon distending pressure. The duration of colorectal distension was limited to < 25 minutes per experiment. Experiments involving ≥ 15 minutes of colorectal distension were performed no more than twice per week in an individual rabbit. Pressure in the colorectal balloon was decreased or released if rabbit shows signs of severe discomfort, sustained increases in mean arterial pressure of greater than 25 mmHg above baseline, or vocalization. However, no rabbits have shown any of these signs.

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Rabbits sat quietly in the rabbit box following balloon catheter placement. No rabbits exhibited behavioral signs of pain or distress during or after a colorectal distension experiment, after the balloon was removed, or when observed in their home cages. Post-mortem examination of rabbits undergoing this procedure reveals no tissue damage.

Based upon the data we have collected during colorectal distension in conscious rabbits, we are confident that this model of visceral pain is short-lived, responsive to opioid analgesia, and causes no lasting tissue damage. In addition, in all experiments, care was exercised to limit the duration of colorectal distension to the minimum time required to complete experiments.

Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results.

Treatment of blood loss in humans and other animals is an important medical problem. Although blood loss in the real world is usually associated with simultaneous stress and/or pain, almost nothing is known about the effects of stress and/or pain on the cardiovascular response to blood loss. We feel that evaluating cardiovascular, respiratory, and central nervous system responses to blood loss in a conscious animal in the presence of environmental stress and pain may best approximate the response to blood loss in a clinical setting. This project investigated this important question. Rabbits served as a model to better understand the response to blood loss in all animals.

In the human and veterinary clinical setting, trauma leading to blood loss is associated with both stress and pain. Thus, evaluation of the cardiovascular and respiratory response to hemorrhage in a conscious animal in the presence of environmental stress and pain may best approximate blood loss in a clinical setting. This project evaluated the effect of pain and stress on the integrated neurohumoral and hemodynamic response to blood loss and therefore required an intact animal model. This project cannot be done with isolated cells or tissues because many cells and tissue types, as well as organ systems, are involved in the response to blood loss. In addition, the normal response to pain requires an intact central nervous system. Thus, we must use intact animals for the studies.

We evaluated the effect of colorectal distension on cardiovascular parameters in halothane-anesthetized rabbits, as well as conscious, chronically instrumented rabbits. While colorectal distension in both conscious and anesthetized rabbits is associated with increased arterial pressure, the response is significantly blunted in anesthetized rabbits. In other words, the physiologic response to pain is altered by anesthesia and acute tissue trauma (surgery). Thus, since our studies were designed to examine the effects of painful sensory

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input on cardiovascular and respiratory control, it is necessary to use conscious, chronically instrumented rabbits.

The effect of pain on cardiovascular and respiratory control during hemorrhage in conscious animals has not been studied. Despite the obvious importance of this area in terms of medical treatment of traumatic injury, our literature searches as well as consultation with experts in this area indicate that the information that comes from this study is new information, which is not presently available. A search of two data bases (Current Contents: 1993 – 2005 & Biological Abstracts: 1980 – 2005) on August 31, 2005 using the keywords "effect of pain and hemorrhage," "effect of pain and response to blood loss," and "effect of pain and cardiovascular control" yielded three unrelated results: 1) Hanaue, H. *et al.* 1987. Postoperative intravenous administration of lysine acetylsalicylate effect on pain relief and platelet function. *Clinical Therapeutics*. 9(2); 159-166. 2) Bancroft, J. and D. Rennie. 1995. Perimenstrual depression: Its relationship to pain, bleeding, and previous history of depression. *Psychosomatic Medicine*. 57(5); 445-452. 3) Bundsen, P. *et al.* 1981. Pain relief in labor by transcutaneous electrical nerve stimulation - a prospective matched study. *Acta Obstetrica et Gynecologica Scandinavica*. 60(5); 459-468.

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